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PROCESS FOR PREPARING PHARMACOLOGICALLY ACTIVE PYRIMIDO (6,1-a) ISOQUINOLIN-4-ONE DERIVATIVES AND THEIR ACID ADDITION SALTS.

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The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed :-

This invention relates to a process for preparing pyrimido(6,1-a)isoquinolin-4-one derivatives of the formula I shown in the drawings accompanying this specification, in which R^1, R^4 and R^5 stand for hydrogen, hydroxy, lower alkoxy, dialkylphosphinylalkoxy, acyloxy or halogen; any two of R^1, R^4 and R^5, when in adjacent positions and taken together form a methylenedioxy or an ethylenedioxy group; one of R^3 and R^6 stands for a pair of electrons and the other stands for alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkylphosphinylalkyl, acyl and optionally substituted aryl denoting an aromatic hydrocarbon group having upto 10 carbon atoms; and R^2 stands for hydrogen, lower alkoxy, alkylamino, dialkylamino, arylamino, alkyl substituted by a 5- or 6-membered carbon ring containing upto 3 hetero atoms selected from the group of N, O and S, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, and optionally substituted aryl denoting an aromatic hydrocarbon group having upto 10 carbon atoms and their acid addition salts.

The present invention provides a process for preparing pyrimido (6,1-a)isoquinolin-4-one derivatives of aforesaid formula I and their acid addition salts, which comprises a tautomeric compound of the formula Ia and/or Ib shown in ...ngs accompanying this specification, in which R^1, ...fined above; one of R^3 and R^6 stands for ...ther stands for hydrogen; R^2 ...ned above with a compound

of the formula RX, wherein R stands for alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkylphosphinylalkyl, acyl and optionally substituted aryl denoting an aromatic hydrocarbon group having upto 10 carbon atoms and X stands for halogen such as chlorine, bromine or iodine or O- C-OR' in which R' is lower alkyl in the presence of a solvent such as herein described and if desired converting the resulting free base into an acid addition salt such as herein described in known manner.

Preferably, the reaction of the tautomeric compound of the said formula Ia and/or Ib with a compound of the said formula RX is carried out in the presence of a base such as herein described or a salt such as herein described.

Preferably, the reaction of the tautomeric compound of the said formula Ia and/or Ib with a compound of the said formula RX is accelerated or completed by heating the reaction mixture to the boiling point of the compound of the said formula RX or the said solvent.

The solvents, are, for example, polar solvents such as dimethylformamide, dimethylsulfoxide, halogenated aliphatic hydrocarbons such as chloroform, alkanols such as methanol, butanol, ketone such as acetone, aprotic solvent such as high boiling ether such as diethylene glycol dimethylether.

In the said formula RX, in the case of R being phenyl, the phenyl nucleus carries appropriate substituents for example electron withdrawing groups like the nitro group in order that the halide has a sufficient reactivity.

Examples of the base are alkali metal carbonate such as potassium carbonate, alkali metal hydride such as sodium hydride, tertiary amine such as triethylamine, acid acceptor or scavenger such as diazobicyclononene. Examples of the salt are metal fluoride such as potassium fluoride.

Examples of the compound of the said formula RX, in which R is acyl and X stands for halogen or O-C-OR', in which R' is lower alkyl, are acyl halide or acyl anhydride in which the acyl group is an alkanoyl group having at most 6 carbon atoms, for example, acetyl or an aroyl group, for example benzoyl, in which the phenyl nucleus carries appropriate substituents for example electron withdrawing substituents like the nitro group in order that the halide has a sufficient reactivity to provide the desired product and the halogen is chlorine in the presence of a base such as alkali metal carbonate such as potassium carbonate or tertiary amine such as triethylamine.

In our Indian patent application no. 147624 (formerly application no. 433/BOM/76) from which this application has been divided out we have described and claimed a process for the preparation of the tautomeric compound of the said formula Ia and/or Ib.

If R^1, R^2, R^4 and R^5 stand for lower alkoxy groups those having upto 3 carbon atoms are suitable.

Suitable acyloxy groups for R^1, R^4 and R^5 are those in which the acyl group is linear or branched C_1-C_6 alkanoyl, for example acetyle, or aroyl, especially benzoyl in which the phenyl nucleus is substituted one to three times by

halogen, nitro, hydroxy, C_1- C_3 alkoxy and C_1-C_3 alkyl.

If R^1, R^4 and R^5 stand for halogen, chlorine is preferred.

Suitable dialkylphosphinylalkoxy groups for R^1, R^4 and R^5 are those in which the alkyl and alkoxy groups carry atmost 3 carbon atoms, for example, dimethylphosphinylmethoxy.

Especially suitable alkylamino or dialkylamino groups for R^2 are those in which the alkyl groups have at most 3 carbon atoms, for example, methylamino or dimethylamino.

Suitable arylamino groups for R^2 are phenylamino groups in which the phenyl residue is substituted one or more times by halogen, for example chlorine, C_1-C_3 alkyl, for example methyl or nitro. A suitable nitrogen-containing heterocyclic amino group for R^2 is, for example, the N-morpholinoamino group.

As alkyl groups for R^2, R^3 and R^6 there can be used those having at most 6 carbon atoms, for example methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec. butyl or tert. butyl.

Suitable cycloalkyl groups for R^2, R^3 and R^6 are those having at most 6 carbon atoms, for example cyclohexyl.

In the case of R^2, R^3 and R^6 being a substituted alkyl group there are used those having upto 6 carbon atoms and substituted by one or two hydroxy or C_1-C_3 alkoxy groups, halogen atoms, for example, chlorine, amino or di(C_1-C_4 alkyl)amino, dialkylphosphinylalkyl, for example dimethyl-phosphinylmethyl.

Examples of aralkyl groups for R^2, R^3 and R^6 are those having at most 8 carbon atoms, in which the aryl group is

mono- or polysubstituted, especially s bstituted one, two or three times by the substituents defi.ed above for R^1.

Suitable heterocyclic alkyl groups for R^2, R^3 and R^6 are, for example, furfuryl and tetrahydrofurfuryl.

Suitable examples of aryl groups for R^2, R^3 and R^6 are phenyl groups optionally substituted one or several times, preferably one, two or three times by halogen, for example, fluorine, chlorine and bromine, C_1-C_3 alkyl and C_1-C_3 alkoxy, for example methyl, ethyl, methoxy and ethoxy, haloalkyl, for example trifluoro methyl, amino or hydroxy, in the latter the hydrogen atom possibly being replaced by an alkali metal, for example sodium.

Suitable nitrogen-containing heterocyclic groups are, for example, pyrrolidino, piperidino, morpholino and piperazi optionally substituted by alkyl, alkoxycarbonyl, aryl or a nitrogen heterocycle, the terms alkyl, alkoxy, aryl and nitrogen heterocycle having the above meaning.

Examples of suitable acyl groups for R^2, R^3 and R^6 are linear or branched C_1-C_6 alkanoyl, such as acetyl or aroyl, such as benzoyl, wherein the phenyl residue is substituted one or several times by the substituents defined above for R^2, R^3 and R^6 when they represent an aryl group.

As salts of the pyrimido(6,1-a)isoquinolin-2-one derivatives of the invention are mentioned, by way of example, those of inorganic or organic acids, for example, the hydrochlorides, hydrobromides, sulfates, phosphates, acetates, oxalates, tartrates, citrates, maleates or fumarates.

Preferred substituents are :
alkoxy for R^1 and R^4, hydrogen for R^5,

C_1-C_6 alkyl or phenyl optionally substituted one to thr
as defined above for R^2,

C_1-C_6 alkyl, cycloalkyl, substituted alkyl, aralkyl,
heterocyclic alkyl, substituted aryl and C_1-C_6 alkanoyl
R^3 and R^6.

Particularly preferred compounds of the formula I al
in the drawings accompanying this specification are :

9, 10-dimethoxy-3-methyl-2-mesitylimino-3,4,6,7-tetrahydr
2H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-2-(N-methyl-2,4,6-trimethylanilino)-6,7-
dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one hydrochloride,

9,10-dimethoxy-2-(N-isopropyl-2,4,6-trimethylanilino)-6,7-
dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one,

9,10-dimethoxy-3-isopropyl-2-mesitylimino-3,4,6,7-tetrahyd
2H-pyrimido(6,1-a)isoquinolin-4-one,

9,10-dimethoxy-2-(N-ethyl-2,4,6-trimethylanilino)-6,7-
dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one,

9,10-dimethoxy-3-ethyl-2-mesitylimino-3,4,6,7-tetrahydro-2H
pyrimido(6,1-a)isoquinolin-4-one,

9,10-dimethoxy-2(N-acetyl-2,4,6-trimethylanilino)-6,7-
dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one.

In the following Table I there are listed some of the
new pyrimido(6,1-a)isoquinolin-4-one derivatives according
to the invention, the structure of which corresponds to
that of the tautomer of formula Ia shown in the drawings
accompanying this specification.

TABLE I

R^5	$R^1 + R^4$	R^3	R^2	melting point of the free base (°C)	Salt	melting point of salt (°C)
H	9,10(OCH_3)$_2$	$-CH(CH_3)_2$	See Fig.1 of the drawings accompanying this specification	182-183	-	-
H	9,10(OCH_3)$_2$	CH_3	See Fig. 1 of the drawings accompanying this specification	-	HCl	189-191 (decomp)
H	9,10(OCH_3)$_2$	$-(CH_2)_3-CH_3$	See Fig. 1 of the drawings accompanying this specification	177-178°	-	-
H	9,10(OCH_3)$_2$	$-CH_2-CH_3$	See Fig. 1 of the drawings accompanying this specification	164-165°	-	-
H	9,10(OCH_3)$_2$	$-\overset{\overset{O}{\|}}{C}CH_3$	See Fig. 1 of the drawings accompanying this specification	210-212	-	-

In the following Table II are listed some of the new pyrimido(6,1-a)isoquinolin-4-one derivatives according to the invention the structure of which corresponds to that of the isomer of the formula Ib shown in the drawings accompanying this specification.

TABLE II

R^3	$R^1 + R^4$	R^6	R^2	melting point of the free bases (°C)	salt	melting point of salt (°C)
H	9,10(OCH_3)$_2$	$-CH_3$	See Fig. 1 of the drawings accompanying this specification	151-152	HCl	198-200
H	9,10(OCH_3)$_2$	$-CH(CH_3)_2$	See Fig. 1 of the drawings accompanying this specification	178-179	-	-
H	9,10(OCH_3)$_2$	$-CH_2P(CH_3)_2$	See Fig. 1 of the drawings accompanying this specification	-	HCl	208-211
H	9,10(OCH_3)$_2$	$-CH_3$	2,6-dimethylphenyl	-	HCl	202-203
H	9,10(OCH_3)$_2$	$-CH_3$	2,4-dimethylphenyl	-	HCl	203-206(decomp)
H	9,10(OCH_3)$_2$	$-CH_2-CH_3$	See Fig. 1 of the drawings accompanying this specification	142-143°	-	-

R^5	R^1 + R^4	R^6	R^2	melting point of the free bases(°C)	salt	melting point of salt (°C)
H	9,10(OCH_3)$_2$	$-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2NMe_2$	See Fig. 1 of the drawings accompanying this specification	145-146°	-	-
H	9,10(OH)$_2$	CH_3	See Fig. 1 of the drawings accompanying this specification	-	HBr	303-302

The pyrimido(6,1-a)isoquinolin-4-one derivatives of the said formula I possess valuable pharmacological properties, for example, blood pressure lowering properties as demonstrated in cats and dogs, bronchodilatory properties as demonstrated by antagonism to histamine induced bronchoconstriction in guinea pigs, anti-allergic properties as demonstrated by the inhibition of passive cutaneous anaphylaxis (pca) in rats and local anaesthetic properties.

Owing to the hypotensive activity the novel compounds are suitable for the treatment and prevention of heart and circulatory diseases, for example essential and malignant hypertonia, heart insufficiency, Angina pectoris and disturbances of the peripheral circulation. The novel compounds can also be used in combination with other pharmacologically active substances, for example with diuretics, antiarrhythmic agents, β-blockers, tranquilizers, heart vasodilating agents and hypolipidemics.

Because of their bronchodilatory and antiallergic effect, the novel compounds can be used for the treatment and prevention of diseases of the respiratory system, for example bronchial asthma, chronic bronchitis, emphysema and allergies such as allergic asthma, hay fever, allergic rhinitis conjunctivitis uticaria. The novel compounds can also be used in combination with other pharmacologically active substances such as corticosteorids, sympathominetics, xanthine derivatives, antihistamines, tranquilizers, cardiac stimulants .

The active substances according to the invention can be administered perorally, parenterally (intramuscularly, intravenously, subcutaneously), rectally or topically, optionally in the form of an aerosol.

The following doses are used in mammals, particularly man; to reduce the blood pressure; a daily dose of 0.1 to 200 mg. dosage unit 0.1 to 25 mg; as bronchospasmolytic and antiallergic agent; a daily dose of 1 to 500 mg. dosage unit 1 to 100 mg.

The novel compounds can be administered either per se or in admixture with pharmacologically tolerable carrier materials. For administration the active compounds are mixed with the usual aids and transformed into the usual form of administration, for example push-fit capsules, aqueous alcoholic or oily suspensions or solutions. Suitable inert carrier materials are, for example, magnesium carbonate, milk sugar or maize starch, which can be used with the addition of substances such as magnesium stearate. The compositions can be prepared in the form of dry or moist granules. As oily carriers or solvents vegetable and animal oils can be used, for example sunflower oil or cod-liver oil.

In emergency situation , the active compounds can be administered intravenously. To this end, the active compounds or the physiologically tolerable salts thereof, as far as they have a sufficient solubility, are dissolved in the usual auxiliaries, which may also act as distributing intermediary or buffer.

Physiologically tolerable salts are formed, for example, with the following acids; hydrochloric acid, hydrobromic acid and hydriodic acid, phosphoric acid, sulfonic acid, methylsulfuric acid, amidosulfonic acid, nitric acid , tartartic acid, lactic acid, malonic acid, fumaric acid, oxalic acid, citric acid, malic acid, mucic acid, benzoic acid, tannic acid, aceturic acid, embonic acid, naphthalene-1,5-disulfonic acid, ascorbic acid, phenylacetic acid, p-aminosalicyclic acid, hydroxyethane-sulfonic acid, benzene-sulfonic acid or synthetic resins containing acid groups, for example those having an ion exchange effect.

Suitable solvents for intravenous administration are, for example, water, physiological sodium chloride solution or dilute alconols such as ethanol propanediol or glycerol; furthermore sugar solutions, such as glucose or mannitol solutions, or a mixture of the aforesaid solvents

The following examples illustrate the invention.

EXAMPLE 1

a) 9,10-Dimethoxy-3-methyl-2-mesitylimino-3,4,6,7-tetrahydro-2H-pyrimido(6,1-a)isoquinolin-4-one and its hydrochloride

and

b) 9,10-dimethoxy-2-(N-methyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one and its hydrochloride

A suspension of 9,10-dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one (3.0 g), anhydrous potassium carbonate (15.0 g) and methyl iodide (45.0 ml) in acetone (300.0 ml) is heated under reflux for 15 hours. The reaction mixture is cooled and filtered. The filtrate is concentrated under reduced pressure whereby a residue is obtained. Chromatography of the residue on silica gel using benzene-chloroform (1:1) as eluent gives the desired free bases a) 2.3 g, m.p. 151-152° and b) 0.15 g, m.p. 175-176°C. The hydrochlorides are prepared from the bases by dissolving the free base in dichloromethane and treating the solution with a solution of etheral hydrochloric acid. They are crystallized from dichloro-methane/petroleum ether (b.p. 60-80°C) or dichloromethane/ethyl acetate or ethanol-diethylether. M.p. of hydrochloride a) 198-200°C, m.p. of hydrochloride b) 189-191°C.

EXAMPLE 2

a) 9,10-Dimethoxy-2-(N-isopropyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one and

b) 9,10-dimethoxy-3-isopropyl-2-mesitylimino-3,4,6,7-tetrahydro-2H-pyrimido(6,1-a)isoquinolin-4-one

9,10-Dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one (5.85 g) and dimethylformamide (30 ml) are added to oil-free sodium hydride (1.5 g). The mixture is heated for

5 minutes to 110°C and then cooled to room temperature. Isopropyl (3.55 g) is added and the whole is heated to 11 °C for 40 hours. After cooling, methanol is added to the reaction mixture and the solvents removed under reduced pressure. The residue is extracted with chloroform, the extract washed with water, dried over sodium sulfate and evaporated to dryness. The residue is chromatographed to give the bases a) m.p. 182-183°C and b) m.p. 178-179°C.

EXAMPLE 3

a) 9,10-Dimethoxy-2-(N-ethyl-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one and

b) 9,10-Dimethoxy-3-ethyl-2-mesitylimino-3,4,6,7-tetrahydro-2H-pyrimido(6,1-a)isoquinolin-4-one

PROCEDURE A :

Example 1 is repeated with the exception that ethyl iodide is used instead of methyl iodide.

PROCEDURE B :

9,10-Dimethoxy-2-(2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one (0.5 g) and potassium fluoride (0.1 g) are added to dimethylformamide (10 ml). The mixture is heated to 100°C for 1 hour and then cooled. Ethyl iodide (0.2 g) is added and the mixture heated to 100°C for 40 hours. The solvent is removed under reduced pressure and the residue worked up as described in Example 2.

The procedures A and B yield the two isomers in different proportions. Free base a) m.p. 164-165°C; free base b) m.p. 142-143°C.

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EXAMPLE 4

9,10-Dimethoxy-2-(N-acetyl)-2,4,6-trimethylanilino)-6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one

To an ice-cold solution of 9,10-dimethoxy-2-(2,4,6-trimethylanilin 6,7-dihydro-4H-pyrimido(6,1-a)isoquinolin-4-one (1.6 g) in chloroform (40.0 ml) is added first triethylamine (1.2 ml) and then dropwise a solution of acetyl chloride (0.64 ml) in chloroform (10.0 ml). The mixture is stirred for 2 hours. The chloroform solution is washed successively with water, sodium carbonate solution and water, and is then dried over anhydrous sodium sulfate. The solution is filtered and the filtrate evaporated to dryness in vacuo. The residue is triturated with diethyl ether to yield the desired compound in solid form. Yield 1.6 g, m.p. 210-212°C (dichloromethane-petroleum ether b.p. 60-80°C).

WE CLAIM :

1. A process for preparing pharmacologically active pyrimido (6,1-a)isoquinolin-4-one derivatives of the formula I shown in the drawings accompanying this specification, in which R^1, R^4 and R^5 stand for hydrogen, hydroxy, lower alkoxy, dialkylphosphinylalkoxy, acyloxy or halogen; any two of R^1, R^4 and R^5 when in adjacent positions and taken together form a methylenedioxy or an ethylenedioxy group; one of R^3 and R^6 stands for a pair of electrons and the other stands for alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkylphosphinylalkyl, acyl and optionally substituted aryl denoting an aromatic hydrocarbon group having upto 10 carbon atoms; and R^2 stands for hydrogen, lower alkoxy, alkylamino, dialkylamino, arylamino, alkyl substituted by a 5- or 6-membered carbon ring containing upto 3 hetero atoms selected from the group of N, O and S, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl and optionally substituted aryl denoting an aromatic hydrocarbon group having upto 10 carbon atoms and their acid addition salts which comprises reacting a tautomeric compound of the formula Ia and/or Ib shown in the drawings accompanying this specification in which R^1, R^4 and R^5 are as defined above; one of R^3 and R^6 stands for a pair of electrons

and the other stands for hydrogen; R^2 stands for the groups mentioned above with a compound of the formula RX, wherein R stands for alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, heterocyclically substituted alkyl, dialkylphosphinylalkyl, acyl and optionally substituted aryl denoting an aromatic hydrocarbon group having upto 10 carbon atoms and X stands for halogen such as chlorine, bromine or iodine or O-C-OR', in which R' is lower alkyl in the presence of a solvent such as herein described and if desired converting the resulting free base into an acid addition salt such as herein described in known manner.

A process as claimed in claim 1, wherein the reaction of the tautomeric compound of the said formula Ia and/or Ib with a compound of the said formula RX is carried out in the presence of a base such as herein described or a salt such as herein described.

A process as claimed in claim 1 or 2, wherein the reaction of the tautomeric compound of the said formula Ia and/or Ib with a compound of the said formula RX is accelerated or completed by heating the reaction mixture to the boiling point of the compound of the said formula RX or the said solvent.

A process for preparing pharmacologically active pyrimido (6,1-a) isoquinolin-4-one derivatives of the formula I shown in the drawings accompanying this specification and

as defined in claim 1 and their acid addition salts substantially as herein described particularly with reference to Examples 1 to 4.

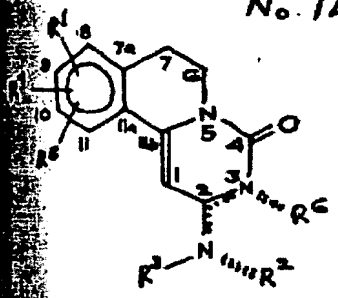
Dated this 13th day of December 1979.

(M.A. Jose)
Of DePENNING & DePENNING
Agent for the Applicant

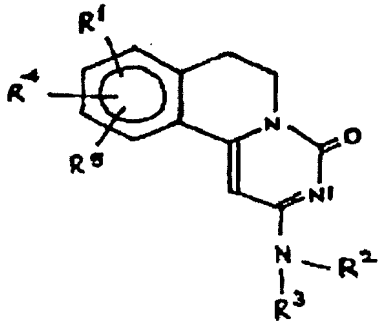
...CHST PHARMACEUTICALS LTD. ...N.F. SHEET,

Complete Specification

No. 1494 5 B.



FORMULA I



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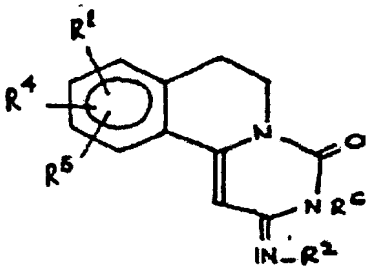

FORMULA Ib

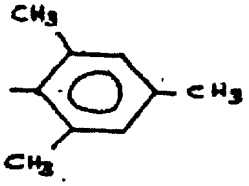

FIG. 1

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